ADVANTAGES OF NEBULISED DRUG THERAPY

When treating various respiratory diseases, inhalation of aerosols to the lungs is the preferred route of administration of pharmaceutical compounds. Unlike pressurised metered dose inhalers (pMDIs) and multidose dry powder inhalers (DPIs), nebulisers can be used across a wide dose range (µg- up to gram-range) without loss of overall delivery performance. Unlike single-breath administration with pMDIs and DPIs, patients take treatment during multiple consecutive spontaneous breathing manoeuvres. Further, the treatment requires only minimal coordination and effort in comparison with pMDIs or DPIs.

Patients with severe disease who experience impaired breathing and co-ordination capabilities can master the use of a nebuliser. Various drug compounds can be nebulised, including peptides (e.g. Colistin), proteins (e.g. alpha-1 antitrypsin), or antibiotics (e.g. tobramycin), and drugs with poor lung tissue penetration (Ciclosporin A). Compared with individual actuations from a pMDI or DPI, nebulisers generate a large amount of fine aerosol which enables the drug to be more evenly distributed to the large surface area of the lungs (best illustrated by “wetting” a tennis court area).

Nebulisers are particularly useful for those drugs which require high dose deposition to the lungs, or for distinct patient populations, such as those with severe disease, young children, the elderly, or mechanically-ventilated patients in a hospital intensive care unit.

While nebulised drugs receive marketing authorisation from the US FDA or European agency (EMA) via a separate new drug application (NDA), nebulisers receive market clearance in the US via a 510(k) premarket notification (CDRH Guideline 784), and by CE marking in the EU. The nebuliser regulatory pathway is advantageous, since inhaled liquid formulations can be tested and clinically evaluated faster and more economically than pMDIs and DPIs. Regulatory approval is usually less burdensome and costly.

ADDRESSING UNMET NEEDS WITH AN ADVANCED AEROSOL PLATFORM: EFLOW®

Looking ahead, the acceptance of nebulisers in a competitive market will require development of improved devices which meet patients’ and caregivers’ needs. Special consideration to superior delivery efficiency with consistent droplet size distribution and dosing during treatment is essential along with treatment times significantly reduced compared with current approved nebuliser therapies. Further, nebuliser features that address ease of use, small size, portability, silent operation, and simple cleaning will help improve patient acceptance to nebuliser therapy.

With the objective of fulfilling these requirements, PARI Pharma developed the eFlow® device platform which utilises a perforated, vibrating membrane technology to generate liquid aerosols of distinct droplet sizes. The eFlow device platform has a significantly higher delivery efficiency than established jet, ultrasonic, or general purpose vibrating-mesh nebuliser systems used with current approved nebulised drug products. The higher delivery efficiency allows for dramatically shorter inhalation times and a substantial reduction of drug volume and
dose, as higher drug concentrations are feasible and less drug is wasted.

Where the approved nebulised drugs of today focus on volume fills of 2-5 ml (7 min up to 30 min range), the targeted formulations of the future in eFlow Technology devices will be in the 0.5-2 ml range (2 min up to 4 min) which encourage improved patient adherence. This feature, qualifies eFlow Technology devices for the delivery of expensive drugs and in situations when long treatment times would be a strong deterrent to patient compliance.

Based on numerous studies and initial market experience, eFlow Technology has proven to be robust and suitable for nebulisation of many drug products including fragile molecules such as rhDNase (Pulmozyme®), alpha-1 antitrypsin, siRNA, DNAzyme, as well as novel liposomal drug formulations.

VERSATILITY FOR CUSTOMISED CONFIGURATIONS

eFlow Technology devices are able to deliver a wide range of drug volumes (0.5-8 ml) and dosages (0.01-1000 mg) and have been customised to meet with dedicated applications and patient requirements. eFlow Technology is attractive for many new and proven drugs as the drug and device are developed and optimised together and approved via mutually conforming labels. Further, eFlow Technology is versatile with respect to target droplet size (mass median diameter (MMD) 2.5 μm up to 5.0 μm) and offers customisation options for lower (lung) and upper (sinus) respiratory drug delivery. eFlow Technology devices are intended for home use as well as the hospital setting, including critical care settings, and are designed as a hand-held version, or as a stationary configuration for use with ventilators (see figure 1). Certain eFlow Technology devices can incorporate an electronic treatment monitoring function to measure compliance.

PROVEN TECHNOLOGY WITH EXCEPTIONAL PATIENT ACCEPTANCE

An eFlow Technology device called eFlow® rapid was designed to deliver comparable doses of currently available nebulised drugs used by cystic fibrosis (CF) patients and approved for use with jet nebulisers, such as the PARI LC PLUS. Since its launch in Europe in 2005, eFlow rapid has gained a market share of about 75% amongst European CF patients. The inhalation of TOBI® (tobramycin) with eFlow rapid has been shown to be safe and effective based on experience from daily practice and a clinical study demonstrating comparable tobramycin blood plasma levels and sputum concentrations.

PIONEERING CHARACTERISATION OF NEBULISED DRUG PRODUCTS

Guidelines issued by the FDA and EMA on nasal and orally inhaled drug products contain testing specifications, but do not disclose how to carry out such tests. An assessment of nebuliser systems cannot be done with a simple gravimetric measurement, but requires the quantification of the drug content delivered under simulated breathing conditions.

The CEN nebuliser standard describes a simplified type-testing method for the head-to-head comparison of nebuliser systems using an aqueous sodium fluoride surrogate solution. However, since physico-chemical properties of solutions and suspensions can deviate substantially from a sodium-fluoride solution, such results do not reflect specific drug/device interactions, especially when delivered using novel aerosol generation technology.

Figure 1: eFlow® Technology platforms: lower respiratory system delivery (eFlow®) and upper respiratory system delivery (Vibrent®)
Thus, the PARI Compas™ Breath Simulator (figure 2) is used for aerosol characterisation testing that allows measurement of the delivered dose of a nebuliser with breath simulation adjusted to realistic patient breathing conditions. The methods used for nebuliser testing (wet aerosols) are substantially different from those established for pMIPs and DPIs (dry aerosols). PARI Pharma was a key contributor to the development of these relevant testing standards which have been implemented for in vitro testing.

**ACCURATE ASSESSMENT OF DROPLET SIZE**

Measurement of nebuliser droplet size is typically conducted using two different methods: laser diffraction or cascade impaction with an Andersen cascade impactor (ACI) or the Next Generation Impactor (NGI). The latter is more suitable since its calibration at 15 l/min allows a more accurate measurement of nebulised aerosols.

In order to avoid droplet evaporation and distortion of the size distribution, proper assessment of the droplet size requires cooling of the impactor for wet aerosols (nebulisers) to equilibrate the temperature of the emitted aerosol. To this end, PARI Pharma developed a climate box allowing adjustment of the temperature of the cascade impactor as well as humidity and temperature of the air entrained into the nebuliser (see figure 3). This set-up allows for the investigation of various effects on the in vitro deposition performance of nebulised products, including effects caused by ambient humidity and temperature as observed with hygroscopic drug compounds.

**UNDERSTANDING DRUG AND DEVICE INTERACTIONS**

Deposition of aerosolised drug into the lungs is determined by different factors, i.e. patient factors and drug/device factors. Individual lung anatomy and patient breathing manoeuvre have a major impact on drug deposition. In addition, the design, functionality and quality of the device and the interaction of drug formulation and device play an important role.

The droplet size can be heavily influenced by the viscosity and surface tension of the drug formulation. Hygroscopic drugs, such as di-sodium cromoglycate (DSCG) and colistimethate may absorb water from the ambient air causing particle growth within milliseconds. Thus, the fine particle dose (respirable particles < 5 μm) of a pMDI or DPI can be reduced significantly when hygroscopic drug is exposed to the humidity saturated human airways, while droplets generated by a nebuliser remain relatively stable.

Adequate in vitro testing of a specific drug/device combination is critical to accurately characterising and identifying such complex interactions before proceeding into costly clinical trials.

**FROM BENCH TO CLINIC: DSCG**

In vitro assessment of various DSCG delivery systems, for the treatment of asthma, revealed extremely poor performance of Intal® pMDI and DPI systems, which led to the conclusion that inhaled DSCG may have been underrated in its therapeutic effect.

We hypothesise that in order to achieve a remarkable therapeutic effect in the treatment of asthma, a much higher DSCG dose will be required at the target site, specifically to the mast cells located in the lung periphery. A clinical study was designed to prove this hypothesis comparing standard inhaled corticosteroid therapy with an isotonic DSCG solution administered via a small droplet eFlow Technology device in children above six months of age. Preliminary findings indicate that the DSCG administered via a small droplet generating investigational eFlow may be equally potent due to a higher and more distally deposited lung dose, compared with twice daily inhaled steroids as no therapeutic difference generated by a nebuliser remained relatively stable.

<table>
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<tr>
<th>Product</th>
<th>Lung deposition [mg]</th>
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<th>C_{max} [mg/l]</th>
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Figure 4: Lung deposition of two 99mTC-DTPA labeled tobramycin solutions investigated in a crossover design study in CF patients (n = 16, 8 children, 8 adults) after inhalation of TOBI (300 mg/5 ml) via the PARI LC PLUS and Tobramycin PARI (150 mg/1.5 ml) via an investigational eFlow nebuliser. Data on sputum concentration and C_{max} were obtained from a 28-day safety study in CF patients (n = 76, 38 children, 38 adults).
could be observed after three and six months of treatment, respectively.8

MATCHING DRUG FORMULATION AND DEVICE: INHALED ANTIBIOTICS

Drug formulations and the delivery device can be mutually adapted and matched for optimal characteristics to achieve the desired therapeutic target. Reformulation of known and proven compounds in a liquid format are commercially attractive as they present a relatively low development risk for potential drug product candidates and, thus, have become a preferred pathway for the development of new inhalation products.

The monobactam antibiotic Cayston® (aztreonam for inhalation solution 75mg) from Gilead Sciences was recently approved as a treatment to improve respiratory symptoms in cystic fibrosis (CF) patients with Pseudomonas aeruginosa (P. aeruginosa).

PARI Pharma contributed pharmaceutical formulation development, analytics and aerosol characterisation to optimise the Cayston formulation with the device. The treatment time for this novel inhaled antibiotic therapy is 2-3 minutes compared with the current first-line therapy, which requires 15-20 minutes per dose.10

Another optimised drug/device combination currently in clinical development is a low-volume, high-concentration Tobramycin PARI inhalation solution (150 mg/1.5 ml) for nebulisation via an investigational eFlow nebuliser. The goal of this development was to decrease CF patient treatment burden by shortening the inhalation time to about one quarter, compared with TOBI (tobramycin 300 mg/5 ml) approved for delivery via the PARI LC PLUS jet nebuliser.

Data summarised from a gamma deposition and safety study (figure 4), demonstrated that nebulisation time could be reduced from approximately 16 minutes to four minutes with a similar deposited dose. Due to the higher delivery efficiency of the investigational eFlow device, only 150 mg (instead of 300 mg) of tobramycin was needed to obtain comparable lung deposition11 and sputum concentration, based on data from a safety study conducted in 76 CF patients (38 adults and 38 children) over 28 days.12

The lower C\textsubscript{max} indicates less drug was systemically absorbed which may reduce the potential for undesired ototoxic and nephrotoxic side effects. The shorter inhalation time could help to improve patient compliance and therapeutic efficacy from a long-term perspective.

DRUG PRODUCTS WITH UNIQUE PROPERTIES: INHALED LIPOSOMAL CYCLOSPORINE A

Over the past several years, PARI Pharma has developed a liposomal cyclosporine A (L-CsA) inhalation formulation as its lead proprietary drug product candidate. The formulation consists of unilamellar liposomes, equal to or less than 100 nm in size, that demonstrated a very favourable lung tissue penetration as well as excellent mucosal tolerability in preclinical testing. L-CsA has undergone a successful Phase Ib lung deposition study13 and is currently being investigated in a multicenter, randomised, double-blind, placebo-controlled Phase IIb study for the prevention of bronchiolitis obliterans in lung transplant recipients.

A UNIQUE CONCEPT FOR PRODUCT PROTECTION: EFLOW® CLOSED SYSTEM

Another major advantage of the eFlow Technology platform is the option to use a proprietary blow-fill-seal ampoule containing the ready to use liquid inhalation formulation. A nebuliser with an integrated single-dose ampoule may be ideal for specific indications where ease of handling...
and protection against the use of unauthorised medications are key factors to the regulatory pathway. In addition, this patented ampoule design allows the prevention of generic alternatives even after the original drug patents expire.

The eFlow closed system highlights three unique design features:
1. A single dose ampoule that becomes an integral part of the device
2. The ampoule is required to operate the device
3. The ampoule is automatically opened when locked into the device.  

Thus, a customisation of nebulised drug therapy regarding age or disease or application-specific requirements can be adequately addressed.

**DRUG DELIVERY IN A VENTILATOR CIRCUIT: EFLOW® INLINE**

Aerosol delivery to mechanically ventilated patients is associated with high drug losses, poorly reproducible delivered doses (DD) to the patient, and rather low delivery efficiency (7.7% mean DD at the end of the endotracheal tube). PARI Pharma has developed a nebuliser configuration with an improved performance for ventilator use characterised by a high dose consistency independent of different ventilators and ventilation parameters. This new eFlow Inline device may serve to improve the treatment of ventilator associated pneumonia (VAP) using, for example, nebulised antibiotics in critical-care settings.

**A NOVEL UPPER RESPIRATORY DRUG DELIVERY CONCEPT: VIBRENT®**

The Vibrent was developed to offer a new treatment option for patients suffering from chronic rhino sinusitis (CRS) affecting about 5-10 % of the population worldwide. The Vibrent is a novel device using pulsating airflow and enabling nasal drug delivery to the osteomeatal area and the paranasal sinuses as revealed from a gamma deposition study in 16 volunteers. Of the emitted aerosol, 71.5 ± 13 % deposited in the nose and 7.1 ± 1.4 % of this amount was found in the sinuses.

Compared with nasal sprays, nasal retention and rather low delivery efficiency (7.7% mean DD) at the end of the endotracheal tube). PARI Pharma has developed a nebuliser configuration with an improved performance for ventilator use characterised by a high dose consistency independent of different ventilators and ventilation parameters. This new eFlow Inline device may serve to improve the treatment of ventilator associated pneumonia (VAP) using, for example, nebulised antibiotics in critical-care settings.

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Drug And Device Development Under One Roof

PARI Pharma’s approach to developing new aerosol therapies is to optimize liquid drug formulations to Advanced Aerosol Delivery platforms including eFlow® (lower respiratory) and Vibrent® (upper respiratory). Current programs in development at PARI or with pharmaceutical partners include inhaled therapies for asthma, COPD, cystic fibrosis, VAP, RSV, lung transplantation and AAT deficiency.

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